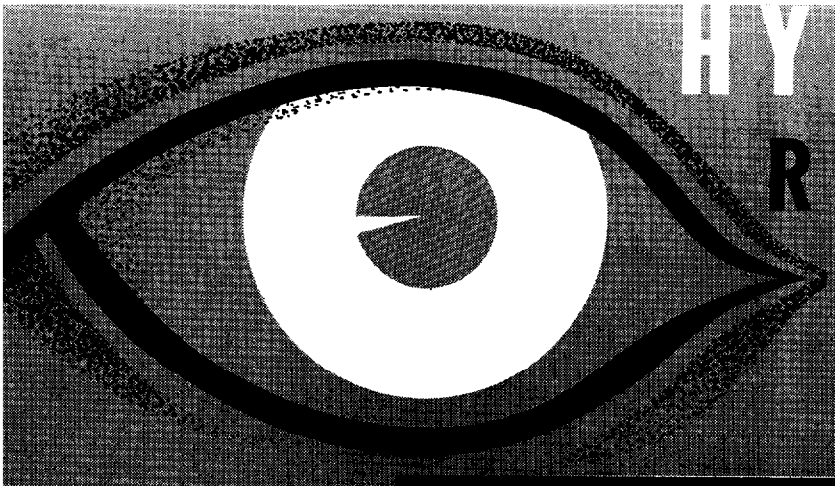
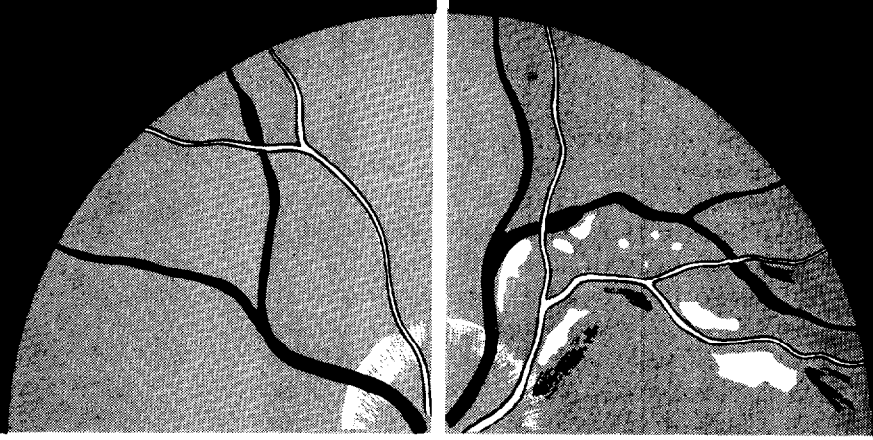
HYPERTENSIV RETINOPATHY



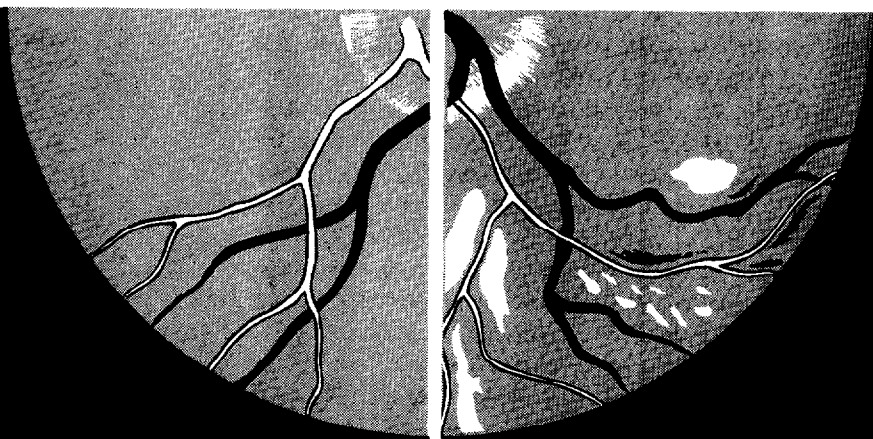
GRADE 3

ADD HEMORRHAGES AND EXUDATES



GRADE 2

GRADE 1 CHANGES PLUS ARTERIOVENOUS COMPRESSION



GRADE 1

ARTERIES BRIGHT AND MODERATELY NARROWED

GRADE 4

ADD PAPILLEDEMA

RECENT DEVELOPMENTS IN THE TREATMENT OF SEVERE HYPERTENSION

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IT SOON becomes apparent to the critical observer that none of the therapeutic methods advocated at present for the treatment of hypertension attacks the fundamental and unknown causes of the disease. Rather they are nonspecific methods of reducing the elevated arterial pressure. Since the etiologic factors are still operating, it is not surprising that reduction of blood pressure cannot be achieved except by rather drastic procedures. This is the reason that sympathectomies must be extensive, that diets must be rigidly restricted, and that hypotensive agents must be potent. Even then the reduction of blood pressure may be only moderate or transient or both.

Evaluation of Significance of Hypertension

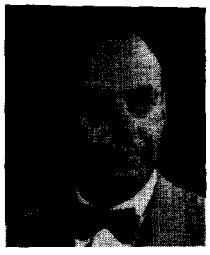
It behooves us, therefore, to examine with care the need for blood pressure reduction in the individual case. We are apt to view with alarm the patient who exhibits a systolic blood pressure of over 200, but does this mean that a calamitous outcome is inevitable? Experience has shown that the level of blood pressure, *per se,* and particularly of systolic pressure is not necessarily associated with a poor prognosis. There are many factors other than the blood pressure level recorded in the office that govern the prognosis, and these factors must be weighed in the balance before deciding on the need for hypotensive therapy.

When hypertension becomes severe it strikes in three vital areas: the brain, the heart, and the kidneys. In the brain a history of cerebrovascular accident or of hypertensive encephalopathy obviously portends further serious difficulties.

Ocular Fundi. Perhaps the most important single prognostic guide is the fundoscopic examination. According to the classification of Keith, Wagener, and Barker, grade I hypertension is associated with moderate narrowing of the arterioles of the optic fundi and is associated usually with a good prognosis. In grade II hypertension the narrowing of the arterioles is more extreme and is associated with compression of the veins at the point of crossing (so-called A-V nicking). In some areas the lumen of the vessels seems completely obliterated, leading to the so-called "silver wire" appearance. The prognosis is variable in this group and often decided by other criteria. In grade III hypertension there is marked arteriolar narrowing and in addition hemorrhages or exudates or both. In this group almost 65 per cent are dead at the end of two years. In the grade IV group, papilledema is present (malignant hypertension), and in this group 79 per cent die within one year.

The examination of the fundi in the hypertensive patient only takes a few moments, and no special training is needed to determine the grade of the hypertension. Only in cases of doubt is it necessary to refer the patient to an ophthalmologist. Because of its great prognostic importance, the fundoscopic examination should be a routine part of the physical examination in all hypertensive patients.

Renal Function. Equally as important as the fundoscopic examination is the estimation of renal damage. The presence of albuminuria, casts, and red or white blood cells indicates active renal deterioration. Many cases of severe hypertension are due to chronic pyelonephritis. If white cells predominate in the sediment, the urine should be



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collected under sterile conditions for culture. Unfortunately, it is very difficult to eradicate a chronic pyelonephritis with antibiotics, and even surgical removal of the infected kidney, when unilateral disease is present, only occasionally is curative of the hypertension. Hence, it is important to treat thoroughly any case of acute pyelonephritis in order to prevent the hypertensive complications of the chronic disease.

Regardless of the cause of the hypertension, the prognosis will depend in large measure on the extent of functioning renal tissue remaining. An estimate of this can be obtained by various renal function tests. Elevation of the nonprotein nitrogen or the urea nitrogen concentration of the blood indicates severe renal impairment. The failure to excrete more than 15 per cent of PSP dye in fifteen minutes after intravenous injection or the failure to concentrate the urine beyond 1.020 after twelve hours of fluid restriction also suggests advanced renal damage. The simplest renal function test is to ask the patient how much nocturia he has. If nocturia has increased within recent months or years, it is likely that the hypertension is severe and that impaired renal function will be found.

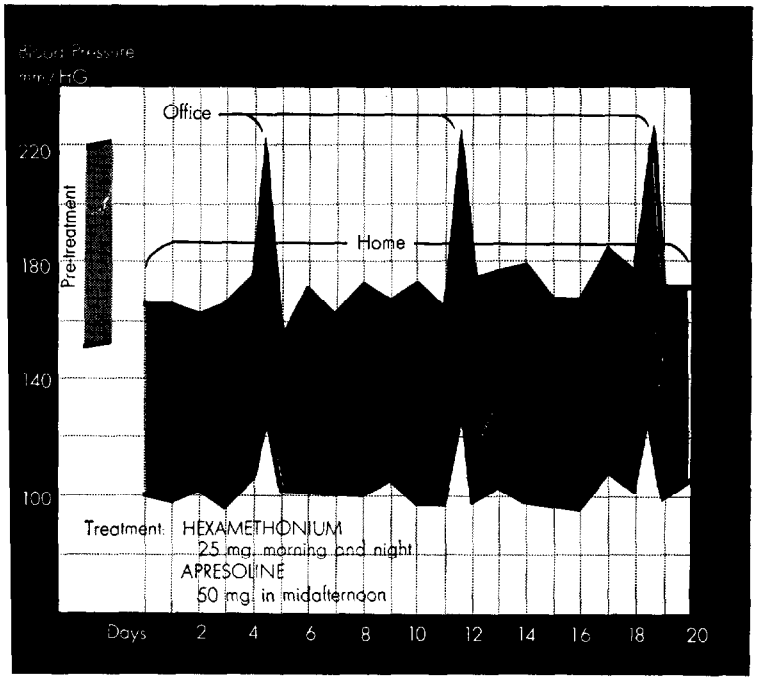

Figure 1. *Comparison of blood pressure recordings at home and in doctor's office. It would be impossible to regulate therapy efficiently on the basis of office blood pressure records alone.*

Cardiac Function. The elevated pressure head in the arterial system increases the work of the heart. Depending on the degree of elevation and its constancy and on the health of the myocardium, the heart may begin to fail after a variable period. The early symptom of such failure is dyspnea on exercise such as climbing stairs or walking up a hill. At a later stage the patient may develop paroxysms of dyspnea which awaken him from sleep at night, or he may develop the classical picture of congestive heart failure.

Height of Blood Pressure. The level of the blood pressure also has considerable prognostic significance, but equally as important is the *lability of the pressure.* If the pressure is excessively high only for brief periods, the prognosis is far better than if it is persistently elevated. Unfortunately the levels recorded in your office may or may not be a true representation of the patient's average blood pressure. It is the often hidden and frequently subconscious apprehension associated with the medical examination which raises the blood pressure far above the basal level. Therefore, when a high level is obtained in a patient who shows no symptoms or signs of severe hypertension in the fundi, kidneys, or heart, the physician may suspect that the blood pressure is labile. This can be confirmed best by admitting the patient to the hospital in order to permit recording of the blood pressure four or five times daily for several days. At times, recording the pressure levels in the congenial surroundings of the patient's home may allay apprehension sufficiently to permit a truer estimate of the average level (*Figure 1*).

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If it has been demonstrated that the blood pressure is not labile, then a level of diastolic pressure of 120 mm. Hg or higher suggests a poor prognosis. Similarly, but to a lesser extent, a persistent level of systolic pressure of 220 mm. Hg or higher in a patient below the age of 65 also suggests a poor prognosis.

The age and sex of the patient are of considerable prognostic importance. The younger the patient for a given level of blood pressure, the poorer the outlook. For some unknown reason, male patients as a rule do not tolerate hypertension as well as females. It is impressive to note the high incidence of severe organic damage in males with hypertension as compared to females.

General Considerations of Treatment

Estimation of Need. At the conclusion of these examinations, it should be possible to determine with fair degree of accuracy the need for intensive therapy. If the fundi show grade III or IV changes, there is no question that therapy is indicated immediately. If the patient develops hypertensive encephalopathy or signs of latent or overt heart failure associated with high levels of blood pressure, the need for therapy is also clearly evident. The presence of sustained levels of diastolic pressure above 120 mm. Hg, particularly when associated with grade II changes in the fundi, albuminuria, cardiomegaly by x-ray, or left ventricular strain pattern by electrocardiography, suggests that treatment at least may be attempted.

But in the absence of such signs of organic strain and in the presence of a labile hypertension, particularly in middle-aged or elderly female patients, usually the best treatment is by reassurance and sedation only. The same may be said for all patients, regardless of age and sex, who show no signs of organic damage and whose levels of blood pressure are 180/110 mm. Hg or less. The reasons for making such a decision in the latter groups of cases are twofold: First, the prognosis usually is good in such patients even when untreated, and second, the treatments available at present for reducing blood pressure are complicated and at times uncomfortable.

Type of Treatment. During the present time there is a gradual but definite trend toward treating severe hypertension with drugs. A trial of chemotherapy involves less expenditure of time and money than surgical sympathectomy and carries lesser risk. While approximately one-third of cases do achieve lowered blood pressure on diets extremely restricted in sodium (200 mg. or less per day), it is very difficult for these patients to remain on such diets for indefinite periods of time. It has been possible, however, to combine less intensive sodium restriction with drug therapy without making life intolerable for the average patient.

Hypotensive Drugs. Once the decision has been made to treat a patient with hypertension, the therapy must be pursued intensively and thoroughly; otherwise the chances of obtaining a successful result are poor. The effective dosages of the presently available agents vary widely in different patients, and frequently they are close to toxic dosages. For this reason adjustment must be carried out even more carefully than with the use of insulin in a diabetic. To prescribe routinely one or two tablets of a hypotensive agent to severe hypertensives is to waste both your time and the patient's.

One of the greatest difficulties in adjusting dosage is that at least half of the cases tend to escape from the hypotensive effects of the drug during the stress of an office visit. As a result when only office pressures are used as a guide to therapy, there is a tendency to increase the dosage beyond the therapeutic range. When toxic effects occur, the physician concludes that the treatment has failed, whereas home blood pressures would have shown that this was not the case.

The ideal method for instituting chemotherapy is to admit the patient to the hospital so that blood

pressures may be recorded before and at suitable intervals after the administration of each dose of a drug. Such a chart provides a reliable index of the patient's response. If the therapy is effective, the patient should obtain a blood pressure apparatus, and a member of the family should be taught to use it so that the response to treatment may be followed after discharge from the hospital. The physician who uses this method will soon find a surprising number of his patients who exhibit much lower blood pressures at home than when they are in the office. He will have a complete record of the response on which to guide his treatment. The situation is somewhat analogous to the home testing of the urine for sugar in diabetic patients.

If the patient is not considered to be sufficiently ill to warrant admitting him to the hospital for regulation, he probably does not require hypotensive drug therapy. However, if home treatment is undertaken, then a member of the patient's family should be instructed in the use of a blood pressure manometer. Home recordings are obtained several times a day for at least a week prior to instituting therapy, and then throughout the dosage adjustment and maintenance periods.

In order for a treatment to be practical it should permit the patient to be gainfully employed if he is physically able. Thus, it seldom is possible to record the blood pressure while the patient is at work, but readings can be taken before and after working hours. Also, it is not possible to use agents with side effects sufficiently troublesome and frequent to force the patient to lose considerable time from his job. However, it is necessary to use potent agents to reduce blood pressure and, as a consequence, a certain number of side reactions are to be expected, particularly during the adjustment period.

Veratrum Viride

Of the drugs more recently introduced for the treatment of hypertension, the veratrum alkaloids have achieved a considerable degree of acceptance. Both the crude powdered plant and the various purified fractions have similar effects.

Hemodynamic Effects. The mode of action has not been established completely. However, it is known that these alkaloids stimulate afferent nerve endings in the heart and carotid sinus which travel to the vasomotor centers to produce a reflex vasodilation and bradycardia. The bradycardia, which is due to vagal stimulation, can be blocked by atropine. The nerve pathways carrying the vasodilator response are still unknown. This reflex stimulation produced by the veratrum alkaloids also may induce other physiologic effects, particularly central nausea and vomiting. It is this latter response which most seriously limits the clinical usefulness of the drug.

The hemodynamic changes following veratrum tend to reverse the pathologic process involved in hypertension. The reduction of blood pressure is accomplished with no reduction of cardiac output, and blood flow through the various vital organs either remains unchanged or is only transiently reduced. There seldom is postural hypotension or other evidences of interference with the homeostatic control of the circulation by the autonomic nervous system.

Toxic Effects. Whereas the incidence of side effects produced by veratrum is high, serious toxicity is rare. No deaths have been reported due to oral ingestion of the drug. Severe hypotension and collapse may occur from overdosage, but complete recovery from these episodes is the rule. From the point of view of toxicity, therefore, veratrum is to be recommended even though discomforting and at times alarming reactions are not rare. The most frequent of these is nausea and vomiting, and for this reason only about one-third of patients can achieve a sustained and significant hypotensive effect without frequent episodes of vomiting.

The emetic dose usually is only slightly in excess of the hypotensive dose. For this reason it is necessary to adjust the dosage very carefully by the method described below. In addition, veratrum produces somewhat of an all-or-none effect; there is no hypotensive response until a critical level is reached, when the hypotension suddenly appears. Therefore, the attempt to produce slight blood pressure falls with small dosages is not successful in severe hypertension.

Dosage Schedules. In actual practice it is best to hospitalize the patient for initial dosage adjustment. At least forty-eight hours and preferably a longer period should be permitted for the blood pressure to level off before beginning treatment. During this and the subsequent period of hospitalization, the blood pressure should be recorded about five times a day by the nursing staff. It is desirable to allow the patient to be up and about the ward during the day.

Dosage is begun at a low level and gradually increased from day to day. Dosages are given after breakfast, at 1:00 or 2:00 P.M., and at bedtime, that is, three times daily. The tendency to vomiting is accentuated if the patient eats during the first four hours after the drug is given. Therefore, the

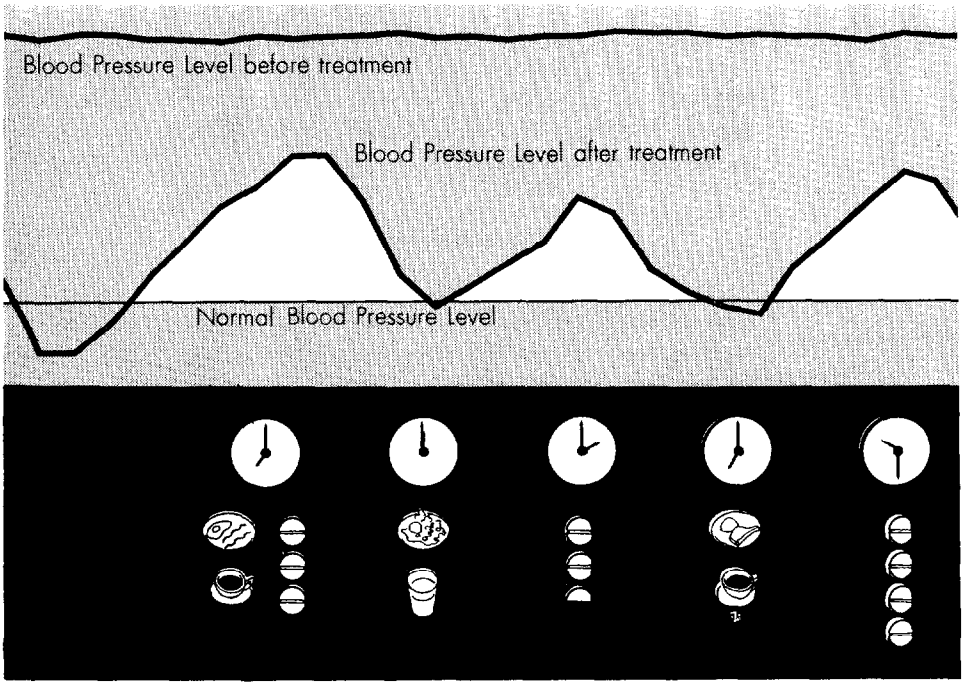

Figure 2. *Diagram of the final dosage regulation in a typical patient with hypertension being treated with a veratrum preparation. The following points are demonstrated: (1) The blood pressure is not maintained at a steady low level but fluctuates downward after each dose of the drug and then rises as the effect passes off; (2) the tablets are given three times daily as close to an eight-hour interval as is practical. However, the patient is not permitted to eat any food for at least four hours after any dose. (3) Because of the longer interval between the night and morning doses, the bedtime dose is larger than the others. Similarly, since the interval between the morning and 2:00 P.M. dose is only seven hours, the 2:00 P.M. dose is the smallest of the day in order to avoid toxicity due to carry-over of the morning medication.*

breakfast should be an early one and the dose taken immediately thereafter. The afternoon dose is taken at 2:00 P.M. if the patient's supper is served at 6:00 P.M. but may be given earlier if the evening meal is served early, as so often happens in the hospital. In order to compensate for the relatively short intervals between the morning and afternoon doses, the afternoon dose usually is smaller than the others, since there will be some residual effect of the morning medication. It also is essential to explain to the patient that dosages and meals should be ingested at the stipulated times in order to avoid toxic reactions. The luxury of late Sunday morning breakfasts must be sacrificed (*Figure 2*).

The regimen used in this clinic is to begin with 1 tablet of any of the veratrum preparations three times daily as described. The blood pressure is recorded immediately before and two hours after each dose, except after the bedtime dose. The next day the blood pressure chart is inspected and the patient questioned for side effects such as epigastric or substernal burning sensation, increased salivation, hiccoughs, or nausea. If there are no side effects and no reduction of blood pressure, the morning and night dosages are raised to 2 tablets, the next day all dosages are elevated to 2 tablets, the next to 3-2-3, and so on until a hypotensive effect or toxic reaction occurs. If a significant fall of blood pressure occurs without side effects, the patient is discharged on that dosage and instructed in recording the blood pressure at home.

Management of Toxic Effects. Not infrequently nausea and vomiting or some other severe reaction, such as marked hypotension and collapse, may occur after several days or weeks at a given dosage level. These toxic reactions usually last for several hours and then pass off without residual effects. During the reaction the patient should be recumbent and atropine, 1 mg., may be administered intravenously or subcutaneously. If hypotension is extreme any of the vasopressor agents except epinephrine may be given. We usually give 50 mg. of ephedrine intramuscularly. Occasional reactions of moderate severity are not unusual during the adjustment period, and the physician should explain the nature of these reactions in advance so that the patient and his family will not be unduly alarmed.

If a reaction occurs it is important to reduce only the offending dose by a small amount, since if all dosages are reduced the therapeutic effect will be lost. If, for example, the patient experiences severe vomiting after the morning dose, this dose only should be reduced by one-half tablet, while the afternoon and evening dosages are not changed. Each time that a severe reaction occurs the offending dose is reduced.

If, on the other hand, there are no reactions and the record of home blood pressure shows a tendency toward elevation to pretreatment levels, dosages should be increased by small increments. In this way, the favorable case gradually attains a maintenance level free of toxic side effects. Should it be

impossible to reduce the blood pressure without recurring toxic reactions, treatment with veratrum preparations must be abandoned, or adjunctive therapy such as a low sodium diet may be added to the treatment regimen.

Hexamethonium

Hemodynamic Effects. Hexamethonium is a potent hypotensive agent which produces its effects by blocking transmission of nervous impulses through all autonomic ganglia. The drug produces postural hypotension by inhibition of the vasoconstrictor reflexes which are activated when an individual assumes the upright posture.

In addition, the drug has parasympathetic blocking effects, including atony of gastrointestinal tract leading to constipation and in rare instances paralytic ileus, loss of visual accommodation leading to blurred vision, loss of salivary secretion producing dryness of the mouth, and failure of penile engorgement leading to impotence. Less frequently observed is failure of contraction of the urinary bladder. Chilling may occur in a cold environment due to failure of reflex vasoconstriction. Fortunately many of these reactions are mild or nonexistent in the individual case, or they disappear as treatment progresses.

Hexamethonium is poorly absorbed from the gastrointestinal tract. In addition the amount absorbed and the duration of the period of absorption seem to be highly variable even in the same patient from day to day. In a given patient, the same dosage may have little or no hypotensive effect on some days, while on others disabling and prolonged hypotension and other evidences of ganglionic blockade may occur. Some days, evidences of drug absorption may be seen one hour after the medication has been given, while on others no effects are observed for four hours or even longer.

In view of these highly unpredictable and hence treacherous responses, we have abandoned the use of oral hexamethonium except for occasional patients who absolutely refuse parenteral administration.

Therapeutic Program. Although the question of the ideal program for administering hexamethonium has not yet been settled, we have been forced to the viewpoint that it is necessary to compromise between the benefits of sustained reduction of blood pressure that might be achieved with hexamethonium and the disadvantages of continuous blockade of the autonomic nervous system with all of the side effects that arise therefrom. Hence, for practical purposes we have resorted to subcutaneous injections of hexamethonium twice daily, or in occasional cases three times daily.

If the patient can obtain a sizable reduction of the average level of blood pressure by two injections a day, treatment is far more practical than when more frequent doses are needed. If he is employed it is possible for him to take his morning dose one hour before the customary hour of arising. The second dose is taken at bedtime, thus leaving the entire day free for him to lead a relatively normal life.

In most patients, however, the blood pressure may return to dangerously high levels by the late afternoon. In such instances we have resorted to the use of a single dose of Apresoline taken by mouth at 3:00 or 4:00 P.M., which will not interfere with the patient's activities.

Hexamethonium effectively lowers arterial pressure in a large percentage of cases, and this reliability is its chief asset. When a quick and fairly certain method for reducing blood pressure is urgently needed, one can usually depend on hexamethonium to do the job. However, the initial dosage must be given with great care. We have seen the blood pressure plummet from 260/160 to 100/80 with as little as 2 mg. of the drug. Subcutaneous administration is just as likely to produce this result as is intravenous administration. Subcutaneous injection is treacherous during this initial dosage period, since a doctor or nurse may not be present when the blood pressure falls to collapse levels.

We have been unable to find any safe method for administering hexamethonium to a patient who has never received the drug previously except by *intravenous* titration, carried out as follows:

1. Dilute the drug with saline in a 10 cc. syringe to a final concentration of 5 mg. per cc.
2. Roll up the head of the bed to an angle of 45°.
3. Have an assistant take the blood pressure in one arm every 30 seconds and read off the values aloud to you. A code may be used if you wish, *e.g.*, 22.5 over 12.5 instead of 225/125.
4. Inject the diluted hexamethonium intravenously at a slow rate of 1 mg. per minute for the first 10 mg. (*Figure 3*).
5. If the blood pressure falls slightly, temporarily stop the injection without removing the needle from the vein. Continue injecting if the reduction is not sufficient. If the reduction of blood pressure is great, the injection is discontinued and the amount given is noted. If there is no appreciable fall after 10 mg. has been given, the rate of administration is

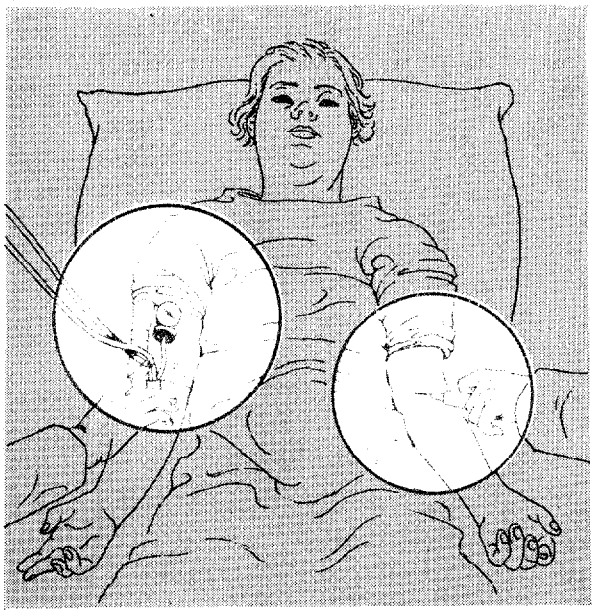

Figure 3. *Method of titrating hexamethonium. Note (1) elevation of head of bed, (2) continuous recording of blood pressure, (3) slow rate of intravenous administration of diluted hexamethonium.*

increased to 2 or 3 mg. per minute until a total of 20 mg. has been given, and then at the rate of 5 mg. per minute until 50 mg. has been given.

6. If there is an excessive fall of blood pressure to collapse level, it is important to act quickly, since the longer the reaction lasts the more difficult it is to reverse. If the bed is rolled down immediately, the pillow removed, the foot of the bed elevated, and the lower extremities raised and massaged without delay, the collapse reaction does not develop to the point of producing subjective discomfort to the patient. The blood pressure will rise almost immediately when the patient is placed in the Trendelenberg position (*Figure 4*). The patient may remain in this position for as long as necessary, usually about one-half hour. The effect of the Trendelenberg position is to return back to the heart the blood pooled in dilated vessels in the lower half of the body. Only rarely is it necessary to use vasopressor agents. If they are used, epinephrine should be avoided.

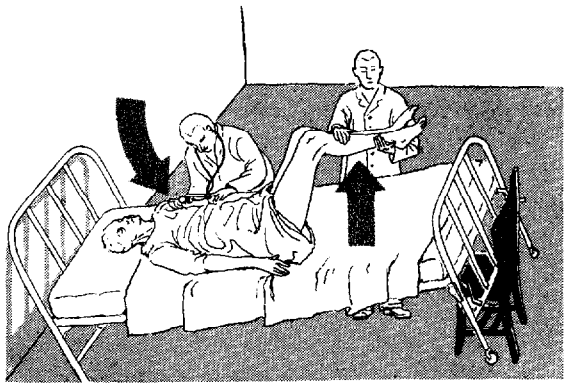

Figure 4. *Method of treating excessive hypotensive reaction in patient receiving hexamethonium*

7. If, as usually happens, a given dosage is found to induce a significant but not excessive reduction of blood pressure, then this full amount is prescribed, to be administered subcutaneously by the nursing staff at 9:00 A.M. and 9:00 P.M. If the blood pressure fall has been excessive, then half of this dose is prescribed morning and night as above. In addition the following orders are written:

(a) Record blood pressure at 9:00 and 10:00 a.m. and 3:00, 4:00, 9:00, and 10:00 p.m.
(b) Roll bed flat for 2 hours after giving hexamethonium. Patient must be told to remain supine throughout this period.
(c) Give Apresoline 25 mg. orally at 3:00 p.m.
(d) Cascara sagrada—4 cc.) at bedtime every night.
Mineral oil—30 cc.) unless there is diarrhea.
(e) If no bowel movement for 48 hours, give s.s. enema.

In a day or two it usually is evident that the initial dose is no longer effective. This is due to the development of tolerance, and dosage must be raised. A good rule for increasing the dosage of hexamethonium is to elevate it by one-half to one-third of the previous dose. Dosage may be raised daily if necessary until the dose is found which will give a consistent response from day to day. Similarly, depending on the blood pressure response or the presence of side effects, the dose of Apresoline may be raised almost daily if need be by increments of 25 mg. to a total dose of 50 to 200 mg. The dosage of Apresoline may be raised whenever the drug appears to lose its effectiveness as judged by a failure of blood pressure fall.

As soon as the dosage becomes stabilized, the patient may begin to attempt to cut down the period of bed rest following the injection. At first he may arise at the end of one and one-half hours. He should try sitting first, then motionless standing beside the bed, since if he begins to feel faint he may lie down immediately. Soon the patient should be able to arise at the end of one hour.

At this time also the patient is instructed, usually by the nursing staff, to administer his own injections. A blood pressure apparatus is purchased and a member of the family is instructed in its use. Some patients are able to take their own blood pressure if they use a snap-on type of cuff and a Bowles type stethoscope which can be inserted under the cuff.

In exceptional cases it has been possible to shorten

the hospitalization period during which this adjustment procedure has been carried out to five days. However, the average case requires ten days. In order to accomplish this, dosages must be adjusted daily if necessary.

After the patient leaves the hospital, he is instructed to return to the office in four or five days and bring with him a list of his blood pressure readings obtained at home during this interval. During the same visit it is worth while to have whoever is recording the blood pressure at home do so in your presence so that you may check on their accuracy.

Nothing is to be gained by a long period of rest at home if the patient is physically able to return to work. If the average daily blood pressure has been lowered to a more benign range, *e.g.*, from 220/130 to 180/110 mm. Hg, and if side effects are not disabling, the patient may return to work. However, the times at which doses of hexamethonium are given must be changed to coincide with an hour before the customary hour of arising, and at bedtime, which may vary from night to night depending on the patient's habits. The time interval between doses need not be twelve hours. Rather every effort should be made to make the schedule as flexible as possible, since the patient will soon tire of observing unnecessary restrictions.

Over a period of succeeding months or years, further elevations of dosage may be necessary particularly in the most severe cases. For example, one of our patients with malignant hypertension required 10 mg. for the initial dose, but after two weeks required 30 mg., and after one year required 125 mg. per dose. No further elevation has been required during the past year. If for any reason either hexamethonium or Apresoline are discontinued for any period longer than three days, it is necessary on beginning treatment the second time to use small dosages. Tolerance tends to disappear when the medication is discontinued.

Conclusion

This review only considers Veratrum and the hexamethonium-Apresoline regimen, because in our experience these have been the most successful and the most practical for long-term treatment of truly severe hypertension. Other drugs may be effective in occasional patients. Indeed placebos frequently will lower blood pressure and relieve symptoms in mild, labile cases. But in the patient with high, relatively fixed diastolic pressure, fundoscopic changes of grade II or more, cardiac enlargement, and early renal impairment, mild "nontoxic" vasodilators are ineffective, and a trial of one or both of the therapeutic regimens outlined above definitely seems indicated.